

efficacy occurs at lower doses than with precursor compounds. See page 40, lines 3-6 of the specification.

Indeed, such unexpectedly improved efficacy has been demonstrated with *in-vivo* experiments as described at Tables 2, 3, and 5 at pages 52, 54 and 57 of the specification, respectively. Regarding such *in-vivo* experiments, Applicants wish to point out that the quantities of tested compounds were on an equal weight basis. Accordingly, the activity data obtained with respect to the nitrooxyderivative of indomethacin (NO-I) refers to a molar quantity that is 30% less than that of the precursor. In addition, the DECLARATION OF DR. PIERO DEL SOLDATO, submitted with the response of August 7, 2002, is relevant to such unexpected improvements, in connection with an experimental model of urinary incontinence. It is further seen through such experiments and experimental model, that the compounds used in the claimed methods of treatment do not result in the disadvantages commonly associated with the precursors.

Applicants point out that the compounds of the claimed invention demonstrate even further advantageous characteristics. For example, such compounds display a lower hypotensive effect than conventional NO donor compounds. This is demonstrated through *in-vitro* experiments, in particular with respect to relaxing activity on vessel smooth muscle. See Examples 13-15 and 13A - 13 B. Applicants point out that in such experiments, the tissue strips were precontracted with phenylephrine and the results evaluated as % inhibition of contractions in the presence of the tested compounds. It is clearly demonstrated that in order to produce a significant hypotensive effect, a molar quantity of NO-I that is 500 times greater, on average, than those of conventional NO donors (cromakalim and nicorandil) was necessary. See

Table 7 at page 60 of the specification. Moreover, it should be noted that the compounds of the claimed invention do not induce tachyphylaxis, that is, the compounds maintain similar effectiveness after repeated administrations. See Table 6 at page 58 of the specification.

Applicants therefore urge that no compound with such unexpectedly advantageous properties has heretofore been described in the prior art. In the Office Action dated October 21, 2002, it was alleged that the present invention as claimed was obvious in view of the combination of precursor (e.g., indomethacin) administered together with a nitric oxide donor. However, Applicants respectfully point out that nowhere in the prior art is there found any teaching or suggestion that such a combination would advantageously and unexpectedly result in a reduction of administered doses, a reduction of hypotensive effect for the NO-donor, and a lack of induction of tachyphylaxis. Indeed, the fact that the present invention as claimed is non-obvious is clearly shown by the data of Table 6 at page 58 of the specification, wherein it is demonstrated that, in contrast to the claimed invention, the combination of precursor and NO-donor proposed in the Office Action results in tachyphylaxis. It is to be noted that the compounds of the claimed invention, for example containing the -
ONO₂ group in particular, are able to address such problems of the prior art, as demonstrated by lower required doses, reduced hypotensive effect and lack of tachyphylaxis.

In fact, Applicants must respectfully submit that those of ordinary skill in the art would have no motivation to arrive at the combination proposed in the Office Action, since the prior art contains not even the slightest teaching or suggestion with respect to the unexpected improvements described above. Applicants point out that the test for

obviousness is not whether some person could have tried a particular combination, but instead whether those of ordinary skill in the art would have been motivated to combine reference teachings so as to arrive at the invention claimed. No such motivation exists in view of the prior art. Moreover, in view of the demonstrated unexpected results for the claimed invention, which find no teaching or suggestion in the prior art, Applicants urge that the claimed invention should be considered patentable at least by virtue of such unexpected results not taught or suggested.

In view of the remarks above, Applicants respectfully submit that this application is in condition for allowance and request favorable action thereon.

In the event this paper is not considered to be timely filed, Applicant hereby petitions for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 01-2300. The Commissioner is hereby authorized to charge any fee deficiency or credit any overpayment associated with this communication to Deposit Account No. 01-2300, referencing Attorney Docket No. 108907-09002.

Respectfully submitted,

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